extensive cross-links along Smc1,3 to map cohesin proximity domains. Mass spectroscopy provided some surprises in that intermolecular cross-links between Smc1,3 extend significantly up from the hinge to link coiled-coil regions [5], reducing the effective lumen size (Figure 1B). EM micrographs similarly document that Smc2,4 coiled coils in condensin complexes remain closely apposed along their length [7,10], despite arguments to the contrary [19].

The most significant obstacle in understanding cohesin function *in vivo* is the lack of a map regarding the path of DNA in/around/through cohesin. To date, the only findings relevant to this question emanate from the SMC-like Mre11,Nbs1,Rad50 complex in which DNA does not pass through the lumen but instead threads between ATPase head domains of Rad50 dimers that are capped by Mre11 dimers [15]. This is a satisfying possibility in which DNA becomes positioned nearest the ATPase domains most likely to exert force (DNA looping for condensin, DNA tethering by cohesin, registration of distal cis DNA elements for transcription) (Figure 1). Regardless, popular models focus on DNA entrapment with Smc1,3 coiled coils. X-ray crystallography mapped Mcd1 binding to a Smc3 head-proximal region of the coiled coil, an 'exit gate' interface through which DNA might escape from cohesin ring entrapment [4,20]. While this remains a viable and important model, expressing amino-to-carboxy terminal fusions of Smc3–Mcd1 (distal from the site mapped above) support cell viability, suggesting that any linkage that closes the ring will suffice [20]. The field looks forward to not only future testing of this model, but considered discussions of any model that appears supported by persistent yet inconvenient truths.

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Neural Coding: Rate and Time Codes Work Together

A new study shows that, when rats discriminate different textures using their whiskers, both spike-rate and spike-timing information in somatosensory cortex contribute to their perceptual decisions. An elegant information theory analysis shows these contributions to be complementary.

Anil K. Seth

Neuroscientists have long wondered about the language of the brain. Do different regions communicate via their neuronal firing rates, by the precise timing of individual spikes, or by some combination of the two? It is well established that both 'rate codes' and 'timing codes' carry information about sensory inputs [1–3], but less clear is whether timing information is used by downstream neural circuits to guide behaviour. Answering this challenging question requires separating the information available in spike rate and in spike timing, and connecting these quantities to behaviour on a trial-by-trial basis. Previous studies have tended to conflate rate and timing information [2,4] and have used information theory to examine how neural responses reflect stimuli, but without always linking these responses to behaviour [1,5]. A new study by Zuo *et al.* [6], reported in this issue of *Current Biology*, takes us forward by showing that spike timing patterns, in both primary and secondary rat somatosensory cortex, make specific trial-by-trial contributions to

perceptual decisions in a texture discrimination task. This finding is important because it directly links timing information in neural spike trains to behaviour, strengthening the case that spike timing plays a causal role in brain function.

Complementary Timing and Rate Information Guide Perceptual Decision

The experimental set up of Zuo *et al.* [6] was conceptually simple. Rats were trained to turn their heads left-or-right to obtain a reward, after sampling a textured plate with their whiskers, with the rewarded direction depending on the texture. After they reached a stable performance level (~77% accuracy) electrodes were implanted and neural responses recorded, during the same task, from both primary (S1) and secondary (S2) somatosensory cortex. Information theory was then used to examine the trial-by-trial relationship between neural activity and stimulus (texture), or behavioural response (correct or error).

The most interesting part of the study is how the data were analysed (Figure 1). For each neuron (or multi-unit), taking all correct trials together, Zuo *et al.* [6] extracted two 'templates': one reflecting the rate information, and another the timing information, carried by the neuron's activity, about the texture. These templates represent the rate and timing 'codes'. The flat 'rate template' had non-zero mean and simply reflected the average spike count following correct decisions. The 'timing template' was constructed using principal components analysis to find the time-varying pattern that best discriminated the different textures, across the trial ensemble. The two templates had the same potential to be informative, preventing bias. Crucially, the timing-template was constructed to have zero-mean, rendering it largely insensitive to rate information. This is what substantiates the authors' claim to have successfully separated timing information from rate information.

Next, considering each (correct) trial separately, Zuo *et al.* [6] compared each spike train with the corresponding template to see which texture was indicated. They also put both templates together in a joint 'rate&timing' code to see whether combining both sorts of information enabled better texture classification. Summarizing across all trials they used information theory to quantify the information provided by each coding scheme (rate, timing, rate&timing) about texture, again for each neuron separately. Their first important finding was that both rate and timing codes carried information about texture, with the timing code carrying slightly but significantly more that the rate code (a difference more pronounced in S1 than in S2). In addition, the information carried by the 'rate&timing' code was close to the sum of the two individual codes, suggesting that rate and timing information carry largely independent signals about texture — more on this later.

To address the key question of whether timing information matters for behaviour, Zuo *et al.* [6] compared correct trials with error trials. Supporting their hypothesis, information carried by all the codes (rate, timing, and rate&timing) predicted behaviour: correct responses were more likely when the code correctly identified the texture. They also found that texture information carried by the timing code predicted behaviour significantly better than that carried by the rate code, and when rate and timing codes indicated different textures, the behavioural response sided more often with the timing code. Together, these findings establish that timing information in spike trains predicts behaviour in a way that is not confounded by rate. They also suggest that timing information may be more highly weighted than rate information in shaping perceptual decision in this task.

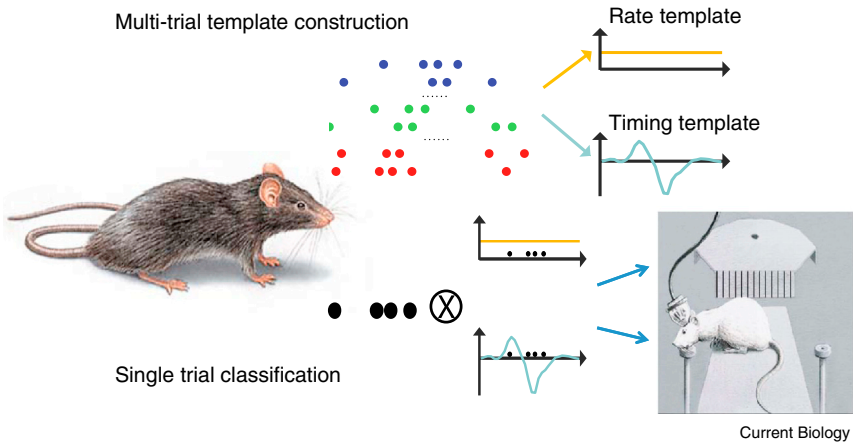

Figure 1. Decoding rate and timing information in a texture discrimination task.

Spike trains are recorded while rats make texture discriminations. The upper part shows how, for each neuron, spike trains from all correct trials are used to construct complementary 'rate' and 'timing' templates. Different colour dots represent neural responses to different textures. The lower part shows how these templates are used to quantify the rate and timing information provided by single-trial spike trains about both the texture presented, and the behavioural response. (Adapted from [6].)

Do Spike-rate and Spike-timing Contribute Independently to Perceptual Decision?

The results of Zuo *et al.* [6] tempt us to conclude that rate-information and timing-information are not just complementary, but that they furnish *independent* contributions to perceptual decision. Supporting this, as mentioned, the texture-specific information in the 'rate&timing' code is more-or-less equal to the sum of the individual codes. As the authors recognize, however, this is not a proof. Trivially, noting the absence of a difference between two quantities is not the same as asserting that they are not different. More interestingly, information-theoretic claims for independent contributions of 'source variables' (here, timing and rate) to 'target variables' (here, stimulus or response) call on *partial information decompositions* (PIDs; Figure 2) [7]. PIDs separate the contributions of two source variables into *unique* components (the information carried by one, but not the other, about the target), *redundant* components (the information shared by both, about the target), and *synergistic* components (the information carried by both

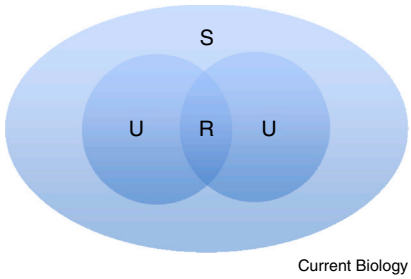

Figure 2. The general structure of a partial information decomposition [7].

The two inner discs represent two 'source' variables that may carry information about a target (not shown). Areas marked U represent the unique information that is specific to each source. Area R represents the redundant information shared by each source, and area S represents the synergistic information that both sources carry about the target, over and above their unique contributions.

together, over and above the sum of their unique contributions). In this setting, establishing independence means showing zero redundancy. While the results of Zuo *et al.* [6] are consistent with this interpretation, they are also consistent with the possibility that the contributions of rate and timing are both redundant *and* synergistic.

This may seem a technicality, but the deep point here is that information theory doesn't always behave intuitively. For instance, even simple Gaussian systems can exhibit net synergy [8], and there is not yet consensus on how to decompose PIDS to independently identify redundancy and synergy [7,8]. These points do not diminish Zuo *et al*'s. [6] excellent analysis, they simply highlight that information theory not only provides a powerful means of answering intuitive questions (like independence of codes) but can shape entirely new questions, like those surrounding synergy.

Information in the Brain

Zuo *et al.*'s [6] findings raise many other interesting questions. For instance, 'top-down' (or better, 'inside-out') influences are increasingly emphasized in theoretical accounts of 'predictive perception' based on Bayesian inference [9,10]. While Zuo *et al.* [6] exclude such influences for their data, their design implicitly minimizes any such effects since textures are presented at random. It would be fascinating to extend their approach to designs which induce pre-stimulus expectations [11], which might provide a unique opportunity to examine how the neural processes underlying putative predictive perception manifest in fine-grained spike-timing patterns [12]. Such extensions could also provide new perspectives on the constitutive role of action in perception [13], which is particularly evident in whisker-based perceptual decision.

Other issues involve distinguishing correlation from causation. Zuo *et al.*'s [6] results show impressive correlations between specific types of information and behaviour, but they do not directly establish that this information plays a causal role within the rat itself. This is an intrinsic feature of information theoretic analysis, which rests on Shannon's original definition of information as observer-dependent. To establish causality would involve, infeasibly, instantiating specific precisely-timed neuronal firing patterns (for example, in S1) while measuring downstream activity and behaviour, and while accommodating the effects of action, 'generative sensation', and other top-down influences. Future optogenetic paradigms may attain this capability but these remain far off. A more feasible alternative would be to examine information *flow* among different regions, again comparing the different coding schemes. Quantities like transfer entropy and Granger causality could be usefully adapted to this purpose [14].

The observer-dependence of Shannon information raises the question of whether there is a neural 'code' — or 'codes' — at all. (More fundamentally: do neurons process information, or is information theory just a way to describe neuronal behaviour?) Certainly, there is no bright line between timing codes and rate codes. High precision timing codes can be re-described as rate codes operating over very short time windows [15]. The loss of reliability that comes from averaging across short windows can be compensated for by considering population responses [16] so that, in some sense, 'population coding' can provide a near-instantaneous readout of firing 'rate'. Here, computational modelling may help. For instance, embodied neuro-robotic models of somatosensory cortex show that population responses can instantiate 'spatiotemporal receptive fields' able to support texture discrimination [17], without specific appeal to coding schemes.

Whether realized in codes or not, neuronal responses — individually or in combination — are likely to encompass the multiple timescales that causally structure embodied interactions with the world [1,18]. Understanding how these timescales are incorporated in neural activity, for instance through hierarchical embedding [18], or multiplexing [19], remains an important challenge. Zuo *et al.*'s [6] elegant study makes a substantive contribution by showing a direct link between precise spike timing and behavioural response, in a temporally structured task, and their paper is essential reading for anyone wanting to learn how to speak 'neuron'.

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Mechanosensing: A Regulation Sensation

Mechanosensing of surfaces in bacteria is a process that often uses obstruction of flagellum rotation to trigger behaviors such as adhesion and surface-associated movement. In a recent publication, the PilY1 protein of *Pseudomonas aeruginosa* has been implicated as a novel mechanosensor that stimulates virulence in response to surface attachment.

Courtney Ellison and Yves V. Brun*

Bacteria utilize diverse strategies for colonizing surfaces to form complex communities. In general, they respond to environmental signals, including nutritional, osmolar, and host-derived cues, activating regulatory circuits that control bacterial behaviors, such as adhesion and biofilm formation [1]. In addition, detection of mechanical stimuli through surface contact, termed mechanosensing, initiates multiple cellular responses that result in surface-associated behaviors, including attachment, movement across a surface, and cellular differentiation [2].

Mechanosensing is a ubiquitous instrument for translating environmental stimuli into biological responses. Organisms respond to gravity, contact with physical barriers, and flow. Some of the most common sensors of mechanical stimuli are ion channels that sense turgor pressure and mechanical tension [3]. In the animal kingdom, von Willebrand factor protein A (vWA) domains act as mechanosensors of flow by detecting shear force, which stimulates unraveling of the von Willebrand factor protein (Figure 1A). This conformational change allows platelets to rapidly bind vWA domains, promote coagulation and stop blood flow when epithelial integrity is breached [4]. In plants, an example of mechanosensation is the touch-based turgor response of the fern species *Mimosa pudica*. Motor organs at the leaf base, called pulvini, induce water loss to initiate leaflet folding upon physical stimulation [5]. However, mechanosensing is not restricted to specialized tissues of multicellular eukaryotes. Here we review what is known about how bacteria use mechanosensing of surfaces to regulate behavior, and we discuss new evidence provided in a recent publication by Siryaporn *et al.* [6] that offers support for another mechanism of surface sensing through mechanical stimulation.

In order to generate appropriate behavioral and regulatory responses to surfaces, bacteria require the ability to sense surface contact. Bacteria can colonize and move across both biotic and abiotic surfaces, with many species using the flagellum as a surface sensor [2]. The flagellum is a rotating, membrane-embedded propeller that drives cell swimming. It obtains energy required for rotation through a proton- or sodium-gradient-generated motive force (P/SMF) that passes through a stationary motor complex called the stator [7]. Because the flagellum is a rotating structure, it provides an opportunity to sense obstruction of its rotation caused by surface contact. Also, an increase in environmental viscosity increases mechanical load on the flagellum independent of surface contact and has been shown to trigger transcription of genes involved in surface-associated functions, such as swarming in *Vibrio parahaemolyticus* [8,9]. Swarming is a complex type of multicellular surface-associated movement that is driven by flagellar rotation [10]. The deletion of the flagellum stator gene *motB* or a filament flagellin subunit gene *flaC* results in constant transcription of genes involved in swarming, indicating that mechanical or genetic perturbation of flagellum function mimics surface sensing [9]. Additionally, disruption of the SMF in *V. parahaemolyticus* using the drug phenamil blocks flagellar rotation and results in a dose-dependent increase in transcription of swarming-related genes in the absence of surface stimulation [11]. An increase in viscosity or the deletion of flagellar structural genes has also been shown to promote cellular differentiation into specialized swarmer cells in *Proteus mirabilis* [12].

The induction of swarming as a result of flagellar inhibition described above suggests a role of flagellar-mediated mechanosensing in regulating surface motility. Other research has implicated a role of flagellar-mediated surface sensing in bacterial adhesion. In *Vibrio cholerae*, chemical perturbation of membrane potential inhibits the transition from reversible to irreversible attachment [13]. In another example, surface contact stimulates secretion of a specialized adhesive polysaccharide involved in irreversible attachment called the holdfast in *Caulobacter crescentus* and the unipolar polysaccharide in *Agrobacterium tumefaciens* [14]. In *C. crescentus*, surface contact and tethering, mediated by both the flagellum and hair-like surface appendages called pili or fimbriae, rapidly inhibit flagellar rotation, resulting in stimulation of holdfast synthesis (Figure 1B). Viscous environments also inhibit *C. crescentus* flagellar rotation and stimulate holdfast production without surface contact and in a pili-independent manner, suggesting that the cell responds